REMARKS

In the Office Action dated December 28, 2009, claims 1-5, 8-34 and 37-47 were pending. Claims 28-29 were withdrawn from further consideration. Claims 1-5, 8-27, 30-34 and 37-47 were under examination and remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher et al. (US 2002/0059652) ("Glimcher") in view of Shaffer et al. (*Immunity*, 2002, 17: 51-62) ("Shaffer"), Pol et al. (*J. Biomol. Screening* 2002, 7: 325-332) ("Pol"), and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307) ('Mountford").

This Response addresses the Examiner's rejection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

In an effort to advance prosecution and without prejudice or disclaimer, Applicants have amended the claims.

Specifically, claim 1 and its dependent claims 2-5 and 8-9 have been amended to delete the reference to "cell" in the preamble. Thus, as amended, claims 1, 2-5 and 8-9, are directed to a genetically modified non-human organism. Claims 48-49 are added, which depend from claim 1 and are supported by previous claim 18-19.

New claim 50 is now directed to a genetically modified cell, as supported by previous claim 1. Claims 13-16 and 19 now depend, directly or indirectly, from claim 50. New claims 51-55, dependent on claim 50, finds support in previous claim 18.

Claim 20 has been rewritten as drawn to a method of identifying antibody secreting cells, as supported by previous claim 26.

Other changes have been made to various claims.

Claims 10-12, 17-18, 21, 26-29 and 40 have been canceled, without prejudice or disclaimer.

No new matter is introduced by the foregoing amendments.

35 U.S.C. §103(a)

Claims 1-5, 8-27, 30-34 and 37-47 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher in view of Shaffer, Pol, and Mountford.

Examiner's Rationale

Glimcher teaches a transgenic mouse comprising a modified *xbp-1* gene encoding functional or non-functional XBP-1 polypeptide co-expressed with a selectable marker or GFP. Glimcher also teaches using the transgenic mouse or B- or T-cells obtained from the mouse to screen for agonists or antagonists of terminal differentiation of B- or T-cells, wherein the test compound modulates the activity of the XBP-1 polypeptide in the B- or T-cells.

The Examiner admits that Glimcher does not teach genetically altering the *Blimp-1* gene or screening for compounds capable of modulating Blimp-1 activity. However, the Examiner notes that the reference teaches that XBP-1 acts downstream of Blimp-1. Additionally, Shaffer allegedly teaches that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp-1 acts by allowing the expression of specific transcription factors such as XBP-1. Therefore, the Examiner concludes that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the cells and method of Glimcher by substituting XBP-1 with Blimp-1 to achieve the predictable result of screening for agonists or antagonists of terminal differentiation of B- or T-cells.

The Examiner admits that Glimcher et al. and Schaffer et al. do not teach inserting a nucleic acid encoding a reporter molecule into an intron of the *Blimp* locus to obtain a modified

blimp allele comprising the Blimp coding sequence and the reporter under the control of the endogenous *Blimp* regulatory elements (claims 1-3 and 30-32). However, the Examiner alleges that Pol supplies such teaching. Further, Mountford teaches using homologous recombination in ES cells to place reporters under the control of regulatory sequences of endogenous genes of interest with or without modifying the endogenous gene, wherein insertion could be within an exon or within an intron.

Examiner's Response To Applicants' Previous Submission

In response to Applicants' previous submission, the Examiner maintains that based on the teachings in the art as a whole, one skilled in the art would have known that XBP-1 acts downstream of Blimp and that, similar to XBP, Blimp is a marker of B-cell terminal differentiation. Further, the Examiner states that the prior art teaches that terminal differentiation of B-cells depends on Blimp, citing Turner et al. (1994) and Angelin-Duclos et al. (2000).

The Claimed Invention

A key feature of the present invention is the specific identification of antibody-secreting cells (ACSs). For example, the present application has demonstrated that the reporter expression is (1) detectable only in ASCs and nearly all ASCs, but not in earlier stages of B cells (see Examples 3-4 on pages 65-67 of the specification); and (2) substantially higher in ASCs than in Blimp1 expressing cells of other haemopoietic lineages (Example 7 on pages 68-69 of the specification). Thus, the present invention is particularly useful for detecting all ASCs (which are a rare cell type).

To highlight this feature of the invention, claim 20 has been amended to recite a method for identifying antibody secreting cells. See also claims 14-15, directed to genetically modified ASCs. Clearly, the genetically modified non-human animal (claim 1 and its dependent

claims) and cells (claim 50 and its dependent claims) permit the practice of the present method for identifying, and optionally further isolating, antibody secreting cells.

As submitted hereinbelow, those skilled in the art would not have had motivation to attempt the claimed invention, and at the very least, would not have predicted or reasonably expected the results achieved by the present invention.

Unobviousness Of The Claimed Invention

The Examiner's premise for concluding the obviousness of modifying the cells and method of Glimcher by substituting XBP-1 with Blimp-1 is that XBP-1 and Blimp are equivalent markers for terminal differentiation, because XBP-1 allegedly acts downstream of Blimp-1.

First, Applicants respectfully reassert that as supported by the Nutt Declaration, it was not possible for one skilled in the art to conclude that XBP-1 acts specifically downstream of Blimp-1. Based on the literature at the time, it is a reasonable conclusion by Dr. Nutt, an expert in the field, that XBP-1 may be expressed upstream and/or downstream of Blimp-1, and/or parallel to Blimp.

Regardless, those skilled in the art would not have considered XBP-1 and Blimp to be equivalent markers so as to substitute XBP-1 in Glimcher with Blimp. As established in the Nutt Declaration, XBP-1 is ubiquitously expressed. See paragraph 4a of the Declaration. See, also, Reimold (2001), previously submitted as Exhibit 3 attached to the Nutt Declaration, page 300, column 2, paragraph 2. On the other hand, the expression of Blimp is more restricted. Thus, the two markers have distinct expression and tissue distribution characteristics.

Further, Applicants respectfully submit that those skilled in the art would not have been motivated to look to the teachings of Glimcher, and to further modify the cells and method of Glimcher by substituting XBP-1 with Blimp-1, and to combine with the teachings of Pol and

Mountford in order to make a transgenic Blimp-reporter mouse. Specifically, based on the literature available at the time, Blimp-1 was known to express in a number of other cell types, including macrophages, granulocytes, monocytic cells, bone marrow-derived macrophages and myeloid cells. See, e.g., Chang et al, Nature Immunol. 2000, submitted in an Information Disclosure Statement filed on October 24, 2006. This is consistent with the showing in the present specification, e.g., Example 7 on pages 68-69. Therefore, the skilled artisan would have expected mixed cell types or multiple cell populations which would display the Blimp-reporter activities in a Blimp-transgenic animal if such animal had been made, which would require additional sorting and analysis for identification. Additionally, there is no indication in the art, including Turner et al. (1994) and Angelin-Duclos et al. (2000) newly cited by the Examiner, that would suggest the percentage of cells within a specific cell type (e.g., ASCs) that would express Blimp. Expression of Blimp in only a fraction of cells of a specific cell type would limit the usefulness of Blimp-reporter-based cell identification. Because of these expected limitations, those skilled in the art would not have been motivated to make such a transgenic animal; or at the very least, would not have had any reasonable expectation that such a transgenic animal would permit the specific identification of ASCs and nearly all ASCs, to the exclusion of other Blimp-expressing cell types.

In contrast, Applicants have demonstrated that in a Blimp1-GFP transgenic mouse, there was a population of cells which exhibited fluorescence to a uniquely high level in the spleen and in the bone marrow, nearly all of which were ASCs. Further, nearly all ASCs were shown to exhibit fluorescence. Thus, using this unique, high level expression of Blimp-controlled reporter approach, all the ASCs were easily identified. As shown in Example 3 (page 65), the isolation of $Blimp^{GFP}$ expressing ASC gives an enrichment of 100,000 fold over unsorted

cells, and provides a virtually definitive method to isolate these rare cells. This result was totally unexpected.

In summation, it is respectfully submitted that those skilled in the art would not have been motivated to rely on the teachings of Glimcher directed to XBP-1, and substitute XBP-1 with Blimp, because those skilled in the art would not have considered Blimp and XBP-1 as equivalent markers. Furthermore, because neither the expression of XBP-1 nor Blimp-1 was limited to a particular cell-type, those skilled in the art would not have been motivated to make a Blimp transgenic animal in order to specifically identify and isolate all ASCs, or at least very least, would not have reasonably expected the successful results achieved by the invention.

Therefore, it is respectfully submitted that the invention, as presently claimed, is not obvious in view of the combination of Glimcher, Shaffer, Pol and Mountford. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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